

EDITORIAL COMMENT

Nonsteroidal Anti-Inflammatory Drugs and Cardiovascular Risk

Is Prostacyclin Inhibition the Key Event?*

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Selectivity toward cyclooxygenase (COX)-2 is usually defined by comparing the capacity of individual nonsteroidal anti-inflammatory drugs (NSAIDs) to inhibit in vitro or ex vivo the generation of thromboxane A₂ (TXA₂) through COX-1 in aggregating platelets with the capacity to inhibit prostaglandin (PG) E₂ generation through COX-2, expressed in leukocytes after an inflammatory stimulus (1). This rather simple test has been regarded as the most useful tool to define a priori the gastric tolerability and potential anti-inflammatory capacity of new NSAIDs, but has turned out to be a criterion to identify potential cardiovascular damage associated with the use of selective or nonselective COX-2 inhibitors and to interpret the results of clinical trials.

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The assumption that COX-2 was primarily involved in the inflammatory response was put into doubt by the finding that this enzyme is implicated in cardiovascular homeostasis. The hypothesis that this is related to inhibition of vasodilatory and antiaggregatory prostacyclin (PGI₂) derives mainly from the seminal observation that administration of selective COX-2 inhibitors results in reduced excretion of a major PGI₂ metabolite (namely, 2,3-dinor-6 keto-PGF_{1α}), a biomarker of synthesis (2). Indirect support has also been provided by showing that deletion or mutation of PGI₂ receptors accelerates the development of atherosclerosis in the presence of vascular injury or cardiovascular risk factors, and allows TXA₂ to exert unopposed prothrombotic activities (3,4). In addition, reduced vascular and renal production of prostanoids by COX-2 may contribute to cardiovascular risk by inducing sodium retention and increasing

arterial pressure, as observed in susceptible subjects treated with NSAIDs (5,6).

When the COX-2 to COX-1 inhibition ratio is calculated, a broad range of values is defined in which one extreme is occupied by the irreversible inhibitor of platelet COX-1 and cardioprotective aspirin (low doses) (7), while highly selective COX-2 inhibitors are found at the other extreme (6).

In some cases, high selectivity toward COX-2 inhibition relates to clinical outcomes and offers a plausible explanation of the underlying mechanism, as is the case of rofecoxib (8). However, in some clinical trials, the incidence of cardiovascular events is not different when drugs with different selectivity toward COX-2 have been compared, as is the case for etoricoxib and diclofenac (9). It may be inferred that other factors related to pharmacodynamics and pharmacokinetics of individual compounds, intensity of treatment, and the clinical characteristics of the studied patients contribute to differences in clinical outcomes. Traditional NSAIDs may show a pattern of COX-2 selectivity similar to that of COX-2 inhibitors, coxibs, as is the case of diclofenac when compared with celecoxib, or may be more active as COX-1 inhibitors, as for naproxen and ibuprofen (6,10).

There is a need to verify the clinical safety of NSAIDs in the absence of randomized placebo-controlled clinical trials regarding the cardiovascular adverse effects of traditional NSAIDs and in light of retrospective studies showing that some NSAIDs are associated with increased cardiovascular risk (11). Indeed, new criteria to identify cardiovascular risk in different therapeutic regimens of individual NSAIDs are needed.

In this issue of the *Journal*, García Rodríguez et al. (12) add substantial new information to this highly debated topic by showing increased cardiovascular risk associated with the use of NSAIDs in clinical practice, and they offer a novel, comprehensive explanation for the observed risk. This was a retrospective case-control study, nested in a population-based data collection, where the end point was myocardial infarction. Patients were treated with traditional NSAIDs or coxibs and were grouped as current, recent, and past users. Attention was also paid to minimization of biases: automated data collection was validated by manual review in a random sample, and new users were identified and evaluated for cardiovascular risk to include early events associated with treatments that could have been missed by studying previously exposed subjects. Exposure to NSAIDs was analyzed taking into account the intensity and duration of treatment as well as the pharmacokinetic characteristics of each individual drug. Overall, a statistically significant increase in relative risk (RR), by 35%, of myocardial infarction was observed; significantly higher values were observed with diclofenac (RR: 1.67) and rofecoxib (RR: 1.47). These results are consistent with those of previous case-control studies and randomized clinical trials (11,13),

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but only partially with the current view that selectivity toward COX-2 is a necessary requirement for cardiovascular risk. In fact, they found that prolonged efficacy and higher doses, and therefore higher levels of active compound, are associated with an increased risk for any given drug. This finding suggests that the degree of COX inhibition by therapeutic levels of NSAIDs should be considered the major determinant of cardiovascular risk (6,12,14).

To test this hypothesis, the authors explored, and found, a correlation between the relative risk of myocardial infarction while a patient was treated with an NSAID and the degree of COX-2 inhibition obtained in vitro using concentrations of NSAIDs similar to those found in vivo at therapeutic doses.

Acting as inhibitors of COX-1, traditional NSAIDs may retain some antiplatelet activity from the inhibition of TXA₂ (6,10,15). However, it is now clear that TXA₂ is extremely effective as a platelet activator, and that its biosynthesis is strictly controlled and only small amounts are actually released in vivo (7,16). Therefore, to prevent the amplification process in platelet activation, the synthesis of TXA₂ must be virtually abolished because residual amounts (approximately 5% of the maximal platelet synthetic capacity) would be adequate to induce the activating signals required for platelet aggregation (7,17). That explains why very few compounds, even when given at adequate, regular doses for prolonged periods, can match the degree of inhibition that is obtained through the irreversible acetylation of COX-1 caused by aspirin (7). This inhibition may occur with therapeutic doses of naproxen, which can reduce the release of TXA₂ from platelets to the same extent reached by aspirin, acting as a reversible inhibitor of COX-1 (15).

From the data presented by García Rodríguez et al. (12), neither naproxen nor ibuprofen increase relative cardiovascular risk, and have either effective anti-COX-1 or poor anti-COX-2 activities. Moreover, the concomitant use of NSAIDs does not appear to increase the risk of myocardial infarction in subjects treated with aspirin, unless competition with certain NSAIDs occurs, thus supporting the concept of the protective effect given by inhibition of TXA₂ biosynthesis in platelets (12). Therefore, increase in cardiovascular risk appears to be indissolubly linked to effective inhibition of COX-2, unless mitigated by the concomitant effective inhibition of platelet COX-1.

The authors propose a model to interpret the epidemiologic data and have devised a test to define a priori both the efficacy and the potential harm of individual NSAIDs. If a drug is unable to determine in vitro at least 95% of inhibition in TXA₂ released from platelets, the cardiovascular hazard increases, provided that COX-2 activity is inhibited by at least 90%. Given that vasculature and COX-2 have been shown to be major sources and catalysts of PGI₂ (6), the authors infer that only a profound reduction in COX-2 activity translates into a substantial reduction in PGI₂ synthesis in vivo, and eventually into increased

risk of myocardial infarction (12). This finding is the most interesting and provocative part of the study. For the first time, numerical data are introduced to analyze (and not merely discuss) the possible link between clinical events and the degree of COX-2 inhibition. Moreover, a threshold is defined, beyond which any further reduction in PGI₂ biosynthesis likely determines vascular dysfunctionality and a prothrombotic state. To reinforce this concept, the authors show in the supplementary data that there is correlation between residual urinary excretion of 2,3-dinor-6 keto-PGF_{1α} after the administration of some NSAIDs and degree of COX-2 inhibition (12).

The proposed paradigm certainly needs confirmation. We do not know when low residual biosynthesis of PGI₂ is actually too low to cause cardiovascular dysfunction or damage, and we do not know whether this threshold is equal in different clinical settings or whether different amounts are required to maintain homeostasis, particularly when the nitric oxide system is defective, as the increased risk observed in patients with previous myocardial infarction may suggest (12). The use of validated biomarkers in relation to measurable cardiovascular phenomena or clinical events may help define the elusive role of vascular COX-2 and PGI₂ in cardiovascular medicine.

The dyad PGI₂-TXA₂ may regain its centrality in the complex picture that has been offered by molecular and pharmacological investigations. Further research is required.

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